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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/021,698	KEITH ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,31-36,41-43,46-59,96-98 and 112-125* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,31-36,41-43,46-59,96-98 and 112-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 July 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/22/03, 2/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the Application filed 22 October 2001 as a continuation of US Patent application 09/881,797, filed 14 June 2001, which claims benefit of provisional application 60/211,749, filed 14 June 2000. The preliminary amendments filed 24 September 2003 have been entered. Claims 1-111 were originally filed. Claims 21-30, 37-40, 44, 45, 60-95 and 99-111 were canceled, claims 1-6, 9, 10 and 41-43 were amended and claims 112-125 were added in the 24 September Paper. Claims 1-20, 31-36, 41-43, 46-59, 96-98 and 112-125 are pending.

Election/Restrictions

Applicant's election with traverse of Group I and SEQ ID NO: 19 with a single G>A polymorphism as set forth as H1 in Table 10 in the reply filed on 24 September 2003 is acknowledged. The traversal is on the ground(s) that the SNP sequences of Table 10 residing within Gene 454 could be searched and examined without undue burden. This argument has been fully considered but is not deemed persuasive because the SNP sequences set forth in table 10 cannot be searched coextensively, and patentability of any individual sequence does not evidence patentability of any other sequence. Therefore, each SNP must be searched and examined independently and examining all of the SNP's together in the same application places an undue burden on the Office.

Applicant additionally argues that SEQ ID NO: 5955, 5957-5958, 5961-5968, 5972, 5974-5975, 5977-5978, 5980, 5982 and 5984 do not change the encoded amino acid sequence and cites MPEP §2434 which states, "Nucleotide sequences encoding the same protein are not

considered to be independent and distinct and will continue to be examined together." This argument is not deemed persuasive because the elected SNP does, in fact, produce a change in the amino acid sequence relative to the sequence encoded by the reference sequence, which amino acid change would not result from any of the other SNP's identified in Table 10. Therefore, the elected nucleic acid sequence does not encode the same protein as is encoded by sequence comprising the other SNP's. Furthermore, claims limited to comprising specific SNP's that do not change an amino acid sequence are not generally directed to any sequence encoding a polypeptide, which is what the statement in MPEP §2434 is referring to. Instead, the SNP's are specific, non-obvious variations within the genus of nucleic acids encoding the protein, which are distinct from one another.

Next, applicant suggests that a search of SEQ ID NO: 19 would encompass the variants set forth as SEQ ID NO: 5955-5984. This argument is not persuasive because most of the claimed sequences are not limited to comprising SEQ ID NO: 19 or having any similarity to SEQ ID NO: 19 beyond comprising the SNP. As the sequences set forth as 5955-5984 are generally less than 50 bases and SEQ ID NO: 19 is >5,000 bases, claimed nucleic acids limited to comprising the SNP's encompass sequences having less than 1% identity with SEQ ID NO: 19. Clearly, a search for nucleic acids having 95% identity with SEQ ID NO: 19, as suggested by applicant, would not adequately uncover all relevant art.

Finally, Applicant argues that the SNP's listed in Table 10 comprise combinations which are associated with asthma and other related diseases. Applicant particularly points out that the specification discloses some SNP combinations have combined p-values <0.1% in gene 454 for the asthma phenotype. This argument is not persuasive because the subcombination represented

by the elected SNP has separate utility as evidenced by its individual p-value <0.1% for the asthma phenotype (Table 12). Applicant appears to be arguing that nucleic acids comprising SNP's disclosed for gene 454 are subcombinations that are useable together. However, subcombinations are distinct from each other if they are shown to be separately usable. See MPEP § 806.05(d).

Applicant's arguments have been fully considered but are not deemed persuasive either individually or as a whole. The requirement is still deemed proper and is therefore made FINAL.

Claims 1-20, 31-36, 41-43, 46-59, 96-98 and 112-125 will be examined to the extent that they read on the elected subject matter of Group I and SEQ ID NO: 19 with a single G>A polymorphism as set forth as H1 in Table 10.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Although the instant application claims benefit of application 09/881,797 in the Declaration, there is no reference to the application in the first line of the specification or in an

application data sheet. Applicant can perfect the priority claim under 35 U.S.C. §120 by amending the first line of the specification as described above.

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, as the provisional application was filed more than one year prior to the filing of the instant application, the instant application is not entitled to benefit of the provisional application. It is noted that, upon perfecting the priority claim under 35 U.S.C. §120 to non-provisional application 09/881,797, which claims benefit of provisional application 60/211,749, the instant application will also be entitled to benefit of the provisional application.

Claim Construction

As an initial matter, it is noted that the nucleic acid sequence as identified as SEQ ID NO: 5969 is disclosed in the specification as the SNP reference sequence (see *e.g.*, page 182, bridging lines 7-8) and according to Table 10 does not comprise the G>A mutation elected in the fourth full paragraph on page 46 of the 24 September Paper. Thus, claims that are directed to nucleic acids comprising SEQ ID NO: 5969, or polypeptides encoded thereby, encompass the reference sequence and exclude the SNP allegedly linked to asthma. As this is clearly inconsistent with the specification and the election in response to restriction, for the purpose of examination and in the interest of compact prosecution the claims are construed such that a recitation of SEQ ID NO: 5969 is understood to refer to the reference sequence set forth in column 5 of Table 10 with the exception that an A is substituted for a G at position 21 resulting in an arginine to histidine substitution (hereinafter referred to as 5969*).

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration on page 5. See 37 CFR 1.52(c).

Drawings

The drawings are objected to because they contain illegible text. Specifically, the margins of Figures 2I, 2K, 2L, 2O, 5B, 5D, 5E, 5F and 5G were insufficient and holes punched in the margins during processing deleted some text. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (*e.g.*, at page 6 and page 92). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claims 1, 3, 5-13, 15-20, 31-33, 35, 36, 43, 56, 58, 96, 97, 113, 115, 116 and 118-125 are objected to because of the following informalities: The claims embrace non-elected subject matter.

Claims 1, 3, 5-13, 15-17, 19, 20, 31-33, 35, 36, 43, 56, 58, 96, 97, 113, 115, 116, 118, 119, 12-, 122, 124 and 125 are directed to nucleic acids and products limited to comprising nucleic acids comprising non-elected SNP's. Reference to non-elected SNP's should be deleted from the claims.

Claims 17-20 and 118-123 are directed to host cells which, interpreted based on the teachings of the specification, encompass the non-elected transgenic animal of Group X. In defining "host" the specification states, "[t]he cells into which have been introduced nucleic acids described above are meant to also include the progeny of such cells". As the specification contemplates genetically modified non-human transgenic animals, which are known in the art to be a progeny of a genetically modified host cell, the skilled artisan would understand the genetically modified transgenic animal to be within the scope of the claimed host cell. This objection can be overcome by amending the claim to recite "isolated host cell" or "host cell *in vitro*".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 96-98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims are directed to isolated antisense nucleic acids comprising nucleic acids complementary to fragments of sequence comprising 5969*. The specification teaches, "antisense nucleic acids or oligonucleotides can inhibit the expression of the gene encoded by the sense strand" (first paragraph on page 40). Thus, the claims are understood to embrace a genus of nucleic acids that are complementary to any fragment of a sequence containing 5969* and capable of inhibiting the expression of a gene encoded by the sense strand.

The Guidelines for Written Description state: "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus" (Federal Register, Vol. 66, No. 4, Column 3, page 1106). "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" (MPEP §2163(3)(a)(ii)).

The art teaches that the ability to inhibit expression of a gene is not a characteristic of all complementary nucleic acid sequences. Far et al. (*Bioinformatics* (2001) 17:1058-1061) teach that the "successful use of [antisense oligonucleotides] to suppress gene expression is somewhat

limited since only a small portion of all possible antisense species against a given target sequence shows efficacy..." (page 1058, column 1, first paragraph of the introduction). Far also teaches that in spite of a considerable amount of empirical data on the use of antisense oligonucleotides, the work "does not seem to be reflected by the knowledge on the biophysical and biochemical level of the action of [antisense oligonucleotides] nor by the knowledge about the rules that govern the relationship between specific sequences of [antisense oligonucleotides], the influence of the target structure, the annealing *in vitro*, and the efficacy *in vivo*" (beginning on page 1058, column 1, third from final line through the fourth line of column 2). Finally, Far teaches, "the effectiveness of [antisense oligonucleotides] is strongly dependent on local target RNA structures, on chemical properties and sequences of the [antisense oligonucleotide] species, and on the characteristics of the biological system of interest including the metabolic properties of the target RNA and the gene product, respectively" (page 1058, column 2, first full paragraph).

A recent article by Braasch *et al.* (*Biochem.* (2002) 41:4503-4510) emphasizes that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (page 4503, first and second paragraphs). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (page 4503, first and second paragraphs). Branch (1998) *Trends Biochem. Sci.* 23:45-50 adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz *et al.* (1996) *Proc. Natl. Acad. Sci. USA* 93:3161-3163 (made of record in the IDS filed 29 July 2003) teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (page 3161, second and third columns). Thus, the art clearly teaches that the disclosure of a sequence does not adequately describe fragments within that sequence having antisense activity as it is defined in the instant application.

Furthermore, the instant application fails to provide a single working example of an antisense nucleic acid within the claimed genus. Thus, it is incumbent upon the specification to disclose the relevant identifying characteristics of a nucleic acids that are complementary to a fragment of a sequence containing 5969* and capable of inhibiting the expression of a gene encoded by the sense strand. However, the discussion of antisense nucleic acids beginning on page 40 of the specification merely provides general teachings such as: "a portion, for example a sequence of 16 nucleotides, could be sufficient to inhibit expression of the protein. Or, an antisense nucleic acid or oligonucleotide, complementary to 5' or 3' untranslated regions, or

overlapping the translation initiation codons...can also be effective" (page 40, second paragraph). These teachings are merely a suggestion as to where the skilled artisan might search for an antisense nucleic acid. The do not describe the relevant identifying characteristics that distinguish a fragment having antisense activity from a fragment that does not have antisense activity. Therefore, the skilled artisan would not view the teachings as sufficient to demonstrate possession of the claimed subject matter.

Although the specification suggests assays that might be used to identify antisense oligonucleotides, adequate written description of an antisense molecule requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the nucleic acid itself. It is not sufficient to define a nucleic acid solely by its principal biological property (*i.e.*, it can inhibit the expression of the gene encoded by the sense strand), because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any nucleic acid with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all nucleic acids that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed

invention. Therefore, the claims fail to meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1-20, 41, 43, 56, 57, 96-98, 113-117 and 119-125 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid comprising 5969* or encoding a polypeptide comprising SEQ ID NO: 111 with the exception of an arginine to histidine substitution at amino acid 270, and vectors and isolated host cells comprising said nucleic acid, does not reasonably provide enablement for the broad scope of the nucleic acids encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The instant claims embrace nucleic acids of tremendous breadth and structural diversity. Independent claims 1 and 2 are directed to a nucleic acid variant encoding a polypeptide, wherein the polypeptide is limited to containing at least one amino acid change which results from the SNP 5969*. Given the broadest reasonable

interpretation of this limitation and the absence of any statement of function in the claims, the claimed nucleic acid is limited only to encoding histidine. Although, the claim recites that the nucleic acid encodes the polypeptide sequence set forth as SEQ ID NO: 111, the claim also recites that there is "at least one amino acid change", which would encompass infinite additional changes.

Similarly, independent claims 5, 6 and 41, which are directed to a nucleic acid comprising SEQ ID NO: 19 containing "at least one" SNP as set forth in 5969*, broadly encompasses any nucleic acid comprising an adenine and infinite additional SNP's.

Independent claim 43 is directed to a nucleic acid comprising 15 contiguous nucleotides of a sequence set forth in SEQ ID NO: 19 which contains "at least one" SNP selected from 5969*, and thus encompasses a fragment of any variant of SEQ ID NO: 19.

The dependent claims are directed to fragments and complementary sequences of the nucleic acids claimed in the independent claims, as well as vectors and host cells comprising the nucleic acids.

State of the prior art and level of predictability in the art: It is generally understood in the art that nucleic acids comprising distinct sequences have distinct functional properties and enablement for one nucleic acid sequence encoding histidine or comprising adenine does not provide enablement for all sequences encoding histidine or comprising adenine. Furthermore, although the instant specification demonstrates that some SNP's present in the P2X7 gene are linked to asthma, the art teaches that linkage of individual polymorphisms within a given gene to a given phenotype must be assessed individually. For example, Blumfeld *et al.* (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While, Blumfeld *et al.* were able to

demonstrate that some of these polymorphisms are associated with patients having asthma, others are not (see Figure 3). For instance, the marker 10-35/390 was demonstrated to be associated with asthma with a p value of 0.00229, while the marker 10-33/327 was determined not to have a statistical association with asthma (p=0.294). It is noted that the data presented in the instant Table 10 demonstrates a similar phenomenon for the P2X7 gene. For example, Table 12A indicates that SNP's such as 454 H 2 and 454 M 2 are not associated with asthma. Thus, the association of a given SNP with a given disease is highly unpredictable even for SNP's within the same gene.

Amount of direction provided by the inventor and existence of working examples: The teachings of the instant specification which are relevant to the elected invention demonstrate that the 5969* mutation in the P2X7 receptor gene is associated with the asthma phenotype (see especially Table 12). The specification further teaches that nucleic acids can be used to diagnose asthma or identify individuals predisposed to developing asthma (discussion beginning on page 73). However, the vast majority of nucleic acids encompassed by the claims would not have sufficient structural similarity to the P2X7 gene comprising the 5969* mutation to be useful as a diagnostic. The specification is silent with regard to how the skilled artisan might use those nucleic acids that encode histidine or comprise adenine but would not function as a diagnostic for the presence of the P2X7 allele comprising the 5969* SNP.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not know how to use those embodiments of the elected invention which do not comprise sufficient structural similarity to the P2X7 allele comprising the 5969* mutation to detect the mutation. As

the claims encompass any nucleic acid comprising the broad structural limitations set forth therein and do not require any particular function, the skilled artisan would have to resort to empirical experimentation divine a use for each claimed embodiment that could not be used as contemplated in the specification. Given the tremendous breadth of the claims the amount of experimentation would clearly be undue.

Claims 31-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and Breadth of the claims: Claims 31-36 are directed to pharmaceutical compositions comprising the claimed nucleic acids. MPEP 2164.01(c) states, "[w]hen a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that use." Thus, enablement for a claimed pharmaceutical requires that the specification teach an enabled pharmaceutical use.

State of the prior art and level of predictability in the art: With regard to the specific therapeutic utility of a nucleic acid comprising the elected SNP, the art does not recognize any link between the P2X7 receptor and any particular disease such that the skilled artisan would know how to administer a pharmaceutical composition comprising the nucleic acid of the claims to achieve a therapeutic outcome. Thus, the skilled artisan is solely dependent upon the teachings in the specification for the manner and process using the claimed pharmaceutical composition, in

such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected use the same.

With regard to general enablement for the pharmaceutical application of nucleic acids, the art teaches that achieving an effective therapeutic outcome was highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, " ... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that, "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the delivery of exogenous DNA and its processing by target cells require the introduction of new pharmakokinetic paradigms beyond those that describe the conventional medicines in use today".

Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3).

In an article published at about the time the instant application was filed, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remained unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches

remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be overcome in the future**", beginning on page 116 and continued through page 125).

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. In that regard, the art is silent with respect to what diseases the skilled artisan might treat using the claimed invention or how the claimed pharmaceutical compositions should be applied to achieve a therapeutic outcome. It should be noted, that Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (page 131, third full paragraph). Thus, absent explicit teachings as to how the specific technical hurdles might be overcome for a specific disease, the skilled artisan must engage in empirical experimentation to overcome the hurdles before the pharmaceutical application of a given nucleic acid is enabled.

Amount of direction provided by the inventor and existence of working examples: In the discussion beginning on page 90 and continued through the first full paragraph on page 93, the specification provides general guidance as to how one might formulate and administer a nucleic acid to a patient. In the discussion beginning in the paragraph bridging pages 96-97, and continued through page 101, the specification also provides general teachings directed to production of constructs for use in gene therapy. However, the teachings provided were routine in the art well before the instant application was filed and do not address the hurdles that the art teaches must be overcome before therapeutic application of nucleic acid pharmaceuticals is enabled.

Beyond these general teachings, the disclosure provides no specific guidance as to how one would use a pharmaceutical composition comprising the nucleic acid of the elected invention. There are no working examples, and there is even no suggestion as to which patient population should be treated using the nucleic acid. The specification discloses that a P2X7 receptor allele comprising a SNP resulting in an arginine to histidine substitution is linked to asthma. However, it is not clear that the mutation itself is the underlying cause of the condition and, even if it were, it is unclear how administering a nucleic acid comprising the mutation would produce a therapeutic outcome. Thus, given the teachings provided in the specification, the skilled artisan would not know what patient population to treat using the claimed pharmaceutical, even if therapeutic application of nucleic acids was generally enabled.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to used the claimed pharmaceutical compositions without undue experimentation. In spite of the art-recognized unpredictability of nucleic acid based therapy and the absence of any teachings in the art directed to therapeutic application of the claimed nucleic acids, the specification provides only general teachings of established therapeutic principles, which had not proved enabling for gene therapy as of the time of filing, and provides no specific guidance with regard to therapeutic application of the elected nucleic acids. Thus, one of ordinary skill in the art seeking to use the claimed pharmaceutical compositions would not only have to overcome the hurdles that have generally hindered the development of nucleic acid therapeutics, but would also have to determine experimentally what patient population might respond to the therapy. Clearly, the amount of experimentation required would be undue. Therefore, the instant claims to

pharmaceutical compositions fail to meet the enablement requirement of 35 U.S.C. §112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20, 31-36, 41-43, 46-59, 96-98 and 112-125 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

First, the claims are indefinite in being directed to "a nucleic acid variant" or compositions comprising said nucleic acid variant. It is unclear how the designation "variant" limits the claimed subject matter. The claims set forth particular limitations that describe a nucleic acid, yet the claim also recites that the nucleic acid is a variant without indicating what properties of the nucleic acid are variant. In particular, "variation" is a relative term, but the claim provides no indication as to the starting point for variation. It would seem that the claims are actually directed to a nucleic acid having the structural properties explicitly set forth in the claim, and the designation "variant" serves no particular purpose. If this were the case, simply deleting the term from the claim would be remedial.

Claims 1 and 2, and claims 3, 4, 13, 14, 33, 34, 113, 114, 119 and 120 as they depend therefrom, are additionally indefinite in reciting that the claimed nucleic acid encodes SEQ ID NO: 111, wherein the amino acid sequence contains at least one amino acid change. If the nucleic acid is limited to encoding SEQ ID NO: 111, it cannot encode a change in the amino acid sequence encoding SEQ ID NO: 111. In other words, a nucleic acid that does not encode SEQ ID

NO: 111 is not within the scope of nucleic acids encoding SEQ ID NO: 111. It would seem that applicant intends to claim a nucleic acid encoding a polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 111, with the exception that the amino acid sequence contains at least one amino acid change. If this were the case, amending the claims accordingly would be remedial.

Likewise, claims 5 and 6, and claims 7-12, 15, 16, 19, 20, 35, 36, 56, 57, 96, 97, 115, 116, 121, 122 and 124 as they depend therefrom, are indefinite in reciting that the claimed nucleic acid comprises the nucleotide sequence as set forth in SEQ ID NO: 19, wherein the nucleic acid comprises at least one single nucleotide polymorphism. It would seem that applicant intends to claim a nucleic acid comprising the nucleotide sequence as set forth in SEQ ID NO: 19, with the exception that the nucleic acid comprises at least one single nucleotide polymorphism, and, if this were the case, amending the claims accordingly would be remedial.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-30, 41-46, 56-59 and 112-125 are rejected under 35 U.S.C. 102(b) as being anticipated by Buel *et al.* (17 October 2000) U.S. Patent No. 6,133,434 (made of record in the IDS filed 22 January 2003).

Buel *et al.* discloses a nucleic acid (*i.e.*, SEQ ID NO: 19) that encodes a polypeptide that is 99.3% identical to the instant SEQ ID NO:111 and further comprises the 5969* arginine to histidine substitution and is 99.5% identical to SEQ ID NO: 19 from nucleotide 48-1896 including the 5969* G>A substitution (see attached sequence alignments). The nucleic acid of Buel *et al.* anticipates the nucleic acid claimed in claims 1-10, 41, 42 and 43.

Buel *et al.* further contemplates complementary nucleic acids according to the limitations of claims 11, 12 and 46 (see especially column 5, lines 61-63), vectors comprising the nucleic acids according to claims 13-16 and 112-117 (see especially column 6, first full paragraph) and transformed host cells according to claims 17-20 and 118-123 (see especially the second full paragraph in column 6). In column 5, line 44, Buel *et al.* teaches that the nucleic acids disclosed therein can be used as probes, and in the first full paragraph in column 8, Buel *et al.* teaches the use of a P2X7 probe and a chemiluminescence detection reagent to detect hybridization, which anticipates the kits of claims 56-59, 124 and 125.

As Buel *et al.* teaches nucleic acids, vectors, host cells, kits and compositions comprising each of the limitations of the instant claims, the claims are anticipated by Buel *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buel *et al.* (*supra*) in view of Maniatis *et al.* (1983) Appendix A: Biochemical Techniques, *in* Molecular Cloning: a laboratory manual, Cold Spring Harbor Laboratory, pp. 461-462.

Although the pharmaceutical claimed pharmaceutical compositions were indicated as lacking enablement due to the failure of the specification to teach the skilled artisan how to use them, applicant is reminded that anticipation of a claimed product requires only that the art teach how to make the product. MPEP 2122 states: "In order to constitute anticipatory prior art, a reference must identically disclose the claimed compound, but *no utility need be disclosed by the*

reference. In re Schoenwald, 964 F.2d 1122, 22 USPQ2d 1671 (Fed. Cir. 1992)" (emphasis added).

Buel *et al.* discloses a nucleic acid that encodes a polypeptide that is 99.3% identical to the instant SEQ ID NO:111 and further comprises the 5969* arginine to histidine substitution and is 99.5% identical to SEQ ID NO: 19 from nucleotide 48-1896 including the 5969* G>A substitution and that the nucleic acids disclosed therein can be used as probes (*Id.*). Buel *et al.* does not explicitly teach that the nucleic acid should be comprised within a pharmaceutically acceptable excipient as contemplated in the first paragraph on page 90 of the specification.

The specification teaches that suitable excipients include, "water, saline, dextrose, glycerol, ethanol, or the like and combinations thereof. In addition, if desired, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH-buffering agents, which enhance the effectiveness of the active ingredient" (page 90, lines 20-24).

Maniatis *et al.* teaches that, when dissolving a DNA pellet, one should use a buffer (see step 7) and that DNA can be easily dissolved in buffers of low ionic strength such as Tris-EDTA (see especially Note iv on page 462).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to dissolve DNA, such as the probe of Buel *et al.* in a buffer, which meets the limitations of the instant pharmaceutically acceptable excipient. Motivation to dissolve the DNA of Buel *et al.* in a buffer comes from Maniatis *et al.* who teaches that DNA is soluble in buffers. Absent evidence to the contrary, one of ordinary skill in the art would also have a reasonable

expectation of success in dissolving DNA in a buffer given the teachings of Maniatis *et al.* indicating that DNA is soluble in a buffer.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DMS

DAVID GUZO
PRIMARY EXAMINER